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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,915	06/27/2003	Stephen L. Hoffman	ABIOS.023A	7068

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/01/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/608,915	HOFFMAN ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-111* is/are pending in the application.

4a) Of the above claim(s) *93-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-92 and 107-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/2006 and 11/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2006 has been entered.

CLAIMS UNDER EXAMINATION

Claims herein under examination are Claims 85-92, 107-111. Claims 1-84 have been cancelled. Claims 93-106 have been withdrawn. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statements filed 12/21/2006 and 11/13/2006 have been considered in full.

INFORMALITIES

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on pages 39, 40, and elsewhere. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

NEW MATTER

Claims 85 and 107-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The instant claims have been amended to generally recite a "second predictive method further comprising comparing the candidate peptide sequence data to the sequence data of the peptide of known affinity." In the response filed 11/13/2006, applicant does not point to support for the newly recited limitation. This limitation, wherein a second predictive method further comprises the step of comparing the candidate peptide sequence data to the sequence data of the peptide of known affinity, is not taught in the specification and is not present within the scope of the original claims as filed. As the newly recited limitations are not supported by the originally filed claims or disclosure, the claims are rejected for reciting new matter. This rejection is necessitated by amendment. Claims 86-89 are also rejected as they depend from claim 85.

CLAIM REJECTIONS - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 85-92 and 107-111 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter. A statutory process must include a step of a physical transformation of matter, or produce a concrete, tangible, and useful result [State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998)], [AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)].

Claims 85-92 and 107-111 are generally directed to methods for assessing the binding affinity between candidate peptides and target proteins, comprising steps directed to obtaining information, determining affinities, scaling affinities, combining affinities, and evaluating affinities These steps do not result in a physical transformation of matter, and encompass non-physical (i.e. *in-silico*) method steps which do not result in a physical transformation of matter. Where a claimed method does not result in a physical transformation of matter, it may be statutory where it recites a result that is concrete (i.e. reproducible), tangible (i.e. communicated to a user), and useful result (i.e. a specific and substantial). In the instant case, claims 85 and 107 result in "evaluating" affinities and therefore do not recite a tangible result such that it is useful to one skilled in the art. For these reasons, the instant claims are not statutory.

This rejection could be overcome by amending the claims to recite that a result of the method is "displayed" or "outputted" (e.g. output to a user, a display, a memory, or another computer, etc.), or by amending the claims to include a step of a physical transformation of

matter (e.g. assay). For an updated discussion of statutory considerations with regard to non-functional descriptive material and computer-related inventions, see the Guidelines for Patent Eligible Subject Matter in the MPEP 2106, Section IV.

CLAIM REJECTIONS - 35 USC §112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 85-92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below which leads to the determination that the above

claim lacks enablement due to undue experimentation being required to make and use the invention.

Claim 85 is generally directed to a method for assessing the binding affinity between a candidate peptide and a target protein, comprising critical steps of (i) obtaining sequence and binding strength data of peptides with known affinity for a target protein, (ii) obtaining sequence data for a candidate peptide, (iii) determining a first affinity using a first predictive method, wherein said first predictive method employs candidate peptide sequence data, (iv) determining a second affinity using a second predictive method, wherein said second predictive method employs candidate sequence data and comprises a comparison of candidate peptide sequence to the sequence of the peptide of known affinity, and (v) scaling and combining said affinities. Claim 90 is directed to a method for evaluating the affinity of a candidate peptide for a target protein, comprising critical steps of (a) obtaining sequence and binding strength data of peptides with known affinity for a target protein, (b) obtaining sequence data for a candidate peptide, (c) determining a first affinity by evaluating sequence and binding information of known peptides and candidate peptides, (d) determining a second affinity by evaluating sequence and binding affinity information for known peptides and candidate peptides. In the instant case, the claimed subject matter lacks enablement for the following reasons:

Both structure-based and sequence-based methods for assessing the binding affinity between candidate peptides and target proteins are well known in the art. With regards to steps (iii) and (iv) above, Yaffe et al. (Nature Biotechnology, April 2001, Vol. 19, p.348-353) teach a sequence-based prediction algorithm for predicting peptides that bind to SH2 and SH3 proteins. Further, the method of Yaffe et al. employs specific model parameters and equations [p.348, Results and Discussion]. Raddrizzani et al. also teaches matrix-based algorithms for predicting peptide/HLA binding interaction that employ specific algorithmic parameters for predicting

protein/peptide binding interaction [p.184, Col. 2, ¶ 3, and Figure 3]. The instant claims do not recite such limitations. The specification fails to disclose or provide working examples as to how first and second predictive methods actually "employ" sequence data in order to determine an "affinity" for candidate peptide and a target protein. Furthermore, the specification fails to disclose or provide working examples as to how the second predictive method "further" compares sequence data of the candidate peptide and peptide of known affinity, and how said comparison is related to said "second affinity" [Wands factors (2), (3)].

With regards to above steps (c) and (d), Rognan et al. teach a structure-based method for assessing the binding affinity between candidate peptides and MHC class I proteins using five different predictive methods to calculate various types of affinities [Fig. 1]. Again, the different predictive methods each comprise specific parameters for determining binding scores (i.e. affinities) based on energy functions specifically related to MHC binding [p.4656, Col. 1 and 2, and Fig. 1]. The instant claims do not recite such limitations. The specification fails to disclose or provide working examples as to how the instant method evaluates both sequence data and binding information in order to determine affinities for candidate peptide and a target protein. It is noted that the specification discloses "voting" or polling heuritstics [0097] that employ binding information [Wands factors (2), (3)].

Given the nature of the instantly claimed invention, one of skill in the art would not know how to practice the claimed invention using the claimed predictive methods without specific guidance as to how said models are actually "employed" (i.e. specific model parameters and sequence information for the appropriate peptide/protein binding), as set forth above in (iii), (iv), (c), and (d). Methods for assessing binding affinity between peptides and target proteins for epitope prediction present several problems depending on the type of method employed (i.e. human or computational), and therefore require sufficient model validation and testing [Mamitsuka, p.460,

Col. 2, and p. 461, Col. 2, ¶1], one skilled in the art would also require undue experimentation to predictably practice the instantly claimed invention [Wands factors (1), (2), (6), (7)].

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 85-89 and 107-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 85 recites the limitation "the binding affinity" (last line of claim 85). There is lack of antecedent basis for this limitation. Claim 85 previously recites "affinity." Correction is requested.

Claim 107 recites the functional limitation "predicting a second binding affinity for the candidate epitope for said MHC protein by using a second predictive method, wherein said prediction comprises a comparison....in order to determine a similarity, and then using the similarity between the two sequences to predict the second binding affinity of the peptide of known affinity." It is unclear in what way the said "similarity" is used to predict the second binding affinity of the peptide of "known" affinity. If is also unclear in what way the prediction of the said second biding affinity of the peptide of "known" affinity results in a prediction of a second binding affinity for the candidate epitope. Clarification is requested.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 85, 87-90, and 92 are rejected under 35 U.S.C. 102 (b) as being anticipated by Yaffe et al. (Nature Biotechnology, April 2001, Vol. 19, p.348-353).

Yaffe et al. teach a peptide-library based searching algorithm that identifies sequence motifs likely to bind to target proteins [Abstract]. More specifically, Yaffe et al. teach the following aspects of the instantly claimed invention:

- Obtaining known peptide sequence data and surface accessibility values (i.e. binding information) [p.353, Col. 1, ¶ 3], as in claim 85, 90.
- Scanning of a protein to obtain potential peptide binding motifs (i.e. candidate peptides), as in claims 85, 90.
- Profile-based scoring algorithm comprising bit scores (i.e. first affinity) calculated for putative motifs domains using a first equation (i.e. first predictive method) [p.349, Col. 1, ¶ 1] that employs sequence information from experimental data [p.353, Col. 1, ¶ 3], as in claims 85, 89, and 92.
- Profile-based scoring algorithm also comprising raw sequence scores (i.e. second affinity) calculated using a second equation [p.349, Col. 1, ¶ 1] and [Fig. 3] that employs

and compares sequence information from putative motifs and experimental data [p.353, Col. 1, ¶ 3], as in claims 85, 90.

- Normalizing (i.e. scaling) bit scores and raw sequence scores [p.349, Col. 1, ¶ 1], which inherently results in values between 0 and 1, as in claims 85, 87, 90.
- Combining normalized raw scores and optimal scores to calculate a final sequence score (S_f), wherein final sequence score is used for assessing the affinity between putative motifs and a target sequence [p.349, Col. 1, ¶ 1], as in claim 85.
- Screening motif wherein motif sequence data is divided into nine-mers or ten-mers [p.350, Col. 2, ¶ 2], as in claim 88.
- Using "final sequence scores" for calculating a percentile rank (i.e. vote) based on said [p.350, Col. 1, ¶ 1] and [Fig. 2], as in claim 90. As final sequence scores inherently contains combined normalized values, the Examiner has interpreted this as a teaching for "combining the first and second votes" as in claim 90.

Claims 85, 86, 90, 91, 107, 109-111 are rejected under 35 U.S.C. 102 (b) as being anticipated by Mamitsuka (Proteins: Structure, Function, and Genetics, 1998, Vol. 33, p.460-474).

Mamitsuka teach supervised learning methods for predicting peptides that bind to MHC molecules [Abstract]. More specifically, Mamitsuka teach the following aspects of claims 85, 86, 90, 91, 107-111:

- Obtaining peptide sequence data and binding information to MHC proteins from MCHPEP database [p.462, Col. 1, ¶3] and [p.464, Results], and generating peptides that are candidates for binding to MHC protein [p.462, Col. 2, ¶ 2], as in claims 85, 90, and 107-111.

- HMM models (i.e. predictive models) are trained on known sequence data for determining similarity between candidate epitopes and MHC molecules [p.467, Col. 2, ¶ 3 and 4], and then applied to unknown epitopes to predict binding affinity of nona-mers based of known information [p. 467, Col. 2, ¶, 5 and 6], as in claims 85, 90, and 107-111.
- Determining forward probability scores (i.e. first affinity) of candidate peptide sequences using HMM (i.e. first predictive method) [p.462, Methods and Materials], wherein scores are scaled between 0 and 1 [Fig. 2], as in claims 85, 90, and 107-111.
- Determining backward probability scores (i.e. second affinity) of candidate peptides sequences using a different HMM (i.e. second predictive method) [p.463, Col. 2 ¶ 2], wherein scores are scaled between 0 and 1 [Fig. 2], as in claims 85, 90, and 107-111.
- Combining forward and backward probabilities [p.463, Equation 2], and real and target probabilities [p.463, Col. 2, ¶ 5], to determine a final probability for candidate sequence, as in claims 85, 90, and 107-111.
- Multiplying all probabilities [p.467, Col. 2, ¶ 5], which also equates to "combining" as in claims 85, 90, and 107-111.
- Evaluating final probabilities to determine the appropriate model for determining binding affinity [p.464, Equation 5], as in claims 85, 90, and 107-111.
- Evaluating binding affinities to determine a ranked list of candidate peptides of nine-residues that bind to MHC proteins [Table III], as in claims 86, 91, and 107-111.

CONCLUSION

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lori A. Clow
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1/22/07

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